Telemedicine Enhanced Asthma Management – Uniting Providers (TEAM-UP)

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Background:

Asthma is one of the most common chronic illnesses of childhood, affecting nearly 10% of children in the US.[1,2] Asthma causes morbidity from recurrent symptoms, impairment of quality of life, limitation of activity, school absenteeism, and missed days of work for caretakers. Asthma also has a significant economic impact; direct health care costs from asthma exceeded $14 billion annually.[3] In the US, children from impoverished and minority ethnic and racial backgrounds suffer disproportionately from asthma.[1,4,5] The US has made a commitment to eliminate health disparities between Black and White Americans, yet numerous studies document disparities in medication use, health care utilization and outcomes in poor and minority patients.[6-11] The goal of asthma therapy is to maintain long-term control (accounting for both the impairment and risk domains) with minimal risk for adverse effects. Inhaled corticosteroids are the most effective long-term therapy for patients with persistent asthma, and are recommended by the NHLBI guidelines as the preferred initial therapy.[12-14] Once inhaled corticosteroids are prescribed, guidelines recommend routine follow-up visits to assess control. [12] Patients who continue to have poor control despite consistent use of a daily inhaled corticosteroid should receive: 1) evaluation and treatment for co-morbid conditions, 2) guideline-based step-ups in treatment, 3) assessment for allergies, with subcutaneous allergen immunotherapy if required, and 4) referrals to community resources for trigger reduction.[12] Children with moderate-severe persistent asthma require 'Step 3' care, with an additional step-up of at least 1 step if asthma remains uncontrolled. The preferred medical treatment for Step 3 care (or higher) is a daily inhaled corticosteroid combined with a long acting $beta_2$ agonist (LABA) or leukotriene receptor antagonist (LTRA), or a medium-dose inhaled corticosteroid.[14-18] Specialist consultation for diagnostic assessment and treatment should be considered for any child requiring Step 3 or higher care, or with mild persistent asthma that is unresponsive to daily preventive therapy.[12]

Despite clear and well-developed guidelines for care, little has been done to assure implementation of these guidelines. Many children in the US with persistent asthma symptoms do not receive recommended anti-inflammatory preventive medications. [19-21] In addition, many children who are prescribed a preventive medication do not achieve optimal control due to poor medication adherence, ongoing exposure to triggers, under-utilization of guideline-based step-wise care by providers, and inadequate access to specialist care leading to suboptimal medication management and untreated co-morbid conditions.[21-24] Importantly, under-treatment is most common among poor urban children. [8,11] Patients who receive care from an asthma specialist are more likely to receive stepwise care consistent with the guidelines, and have improved quality of life and fewer symptoms. [25-28,25-30] However, specialist care is substantially underutilized among urban, African American children,[31,32] perpetuating racial disparities in morbidity. In fact, African American children are sicker compared to white patients before they are seen by a specialist,[31] suggesting delays and disparities in accessing care. There is a clear need for increased access to specialists to optimize guideline based management in urban minority

populations. In our work we have found that adherence to medications is very low,[33] appropriate follow-up occurs infrequently,[34] medications are not optimized,[21] and specialist care is underutilized. School-based programs represent a promising strategy for asthma management because of the ability to optimize children's care in the setting in which they spend most of their day. Further, collaborations with schools provide the opportunity to reach high-risk children and target those in greatest need, regardless of their contacts with the health care system.[35] Over the past 15 years, we have established strong partnerships with schools, providers, and families in the Rochester, NY community, which have allowed us to implement and evaluate programs for urban children with asthma.[35-37] Our prior work demonstrates that school-based directly observed therapy (DOT) of preventive asthma medications can improve outcomes in pediatric asthma, and there is substantial evidence in other therapeutic settings that treatment that is directly observed can be effective.[38-41] By delivering daily preventive medications through schools, adherence can be assured on the days the child attends school, and because schools already routinely provide daily medications for other conditions such as attention deficit disorder, the provision of daily preventive asthma medications represents a conceptually simple system change to improve adherence. Results from our studies have demonstrated reduced morbidity, decreased school absenteeism, and fewer exacerbations.[42-44] We subsequently incorporated communication technology (telemedicine) to enhance the sustainability of this system of care.[36,45] Importantly, there are multiple sites around the country implementing similar models of school-based and even video supported DOT,[46-50] in both research and 'real world' settings, and in Rochester many providers and families now initiate school-based DOT of preventive asthma medications independent of the research program. While these school-based programs consistently improved outcomes for children with persistent asthma, to our concern we have found that not all children benefit to the same degree. Specifically, among the children with moderate-severe persistent or difficult to control asthma at baseline, the majority did not achieve control despite the school based intervention. We realize that our existing programs may be insufficient for these children, since specialist consultation for optimization of medication management or identification and treatment of co-morbid conditions and triggers is not included. In fact, very few of the children in our programs received care from a specialist, trigger exposure was common, and despite follow-up assessments with PCP prompting for guideline-based step-ups in treatments, many of these children were under-treated. We now aim to test a novel school-based program to address these gaps.

Our existing community-wide telemedicine program receives referrals for visits from parents or providers. A Clinical Telehealth Assistant (CTA) collects medical data and images from the child at their school, daycare, or home using mobile units, and stores the data for the provider in a secure internet system. The stored data enable clinicians to provide assessments based on a full complement of clinically-important information. Equally important, providers can engage parents in counseling through remote audiovisual technology. The provider can complete visits from their office at their convenience, and communicate with the caregiver by telephone to collect additional information and discuss the treatment plan. Visits can also be done in 'real-time'; connecting parties via videoconference. The system enables children to be seen by a provider without making a trip to the office, thus eliminating a significant barrier to care.[51,52] Telemedicine visits are reimbursed by local payers, including Medicaid Managed Care (which covers 75% of Rochester's children), making it sustainable. Telemedicine is efficient, cost-effective, and safe, and is now used in urban and rural areas worldwide.[53-55] Telemedicine is also integrated into many school districts, and a systematic review endorsed its use to meet the healthcare needs of underserved children.[56] It can also improve access to specialists, and can be as effective as in person visits for asthma specialist evaluations.[57,58]

Over the past 15 years, we have established strong partnerships with Rochester city schools, providers, and the Rochester community, which have allowed us to implement and evaluate programs for urban

children with asthma. Similar to our prior school-based studies, this current intervention uses a system change to improve the delivery of asthma care. However, it is unique because it targets a particularly high-risk population for whom advanced treatment is needed (urban children with moderate-severe, poorly controlled asthma), and uses telemedicine technology to facilitate access to optimal specialist-directed guideline based step-wise care, in partnership with PCPs and the child's medical home to ensure coordination of care. We will use school-based and video supported DOT to ensure adherence to prescribed therapies. We anticipate that uniting care across settings will optimize treatment for traditionally underserved children with asthma, and ultimately reduce disparities.

This research study is an innovative school-based program for urban children with moderate to severe persistent or difficult-to-control asthma. *The **Telemedicine Enhanced Asthma Management-Uniting Providers (TEAM-UP)** program enhances our school-based, primary care directed asthma program with specialist-supported care to ensure optimal guideline based treatment.* This study is a full-scale randomized trial of TEAM-UP versus an enhanced care comparison group. We will prompt PCPs of all enrolled children (n=360, 4-12 yrs.) to initiate preventive asthma medication and to make a specialist referral. For children in TEAM-UP, the specialist visits will be facilitated via telemedicine. The telemedicine specialist visit will be scheduled after 4 weeks of initiating DOT, in order to allow for accurate guideline-based assessments of medication and care needs once adherence with a daily controller medication is established. There will also be 2 telemedicine follow-up specialist visits to assess the child's response to treatment and make needed adjustments. We will capitalize on the existing community infrastructure by implementing both telemedicine and school-based and/or video supported DOT, and maintaining collaboration with PCPs.

We will also test the feasibility of conducting the TEAM-UP intervention with a small subset of teens (12-16 years) in secondary schools. For this subgroup, we will not prompt PCPs to initiate DOT, but will initiate up to 3 telemedicine visits with an asthma specialist provider.

Study Objectives:

This study has the following objectives:

1. To identify and recruit an urban sample of young children, aged 4-12 years (subset 12-16 years), with moderate-to-severe or uncontrolled asthma from preschool and elementary (subset secondary) schools throughout metro Rochester school districts and from primary care offices that serve children in metro Rochester.
2. To collect baseline morbidity data to characterize this group of children with asthma and to determine risk factors for the frequency and severity of recurrent symptoms.
3. To randomly allocate subjects into either: 1) TEAM-UP intervention group (directly observed administration (DOT) of preventive asthma medications and ongoing monitoring and tailoring of the care regimen using telemedicine directed by specialist care) or 2) a control condition including enhanced care (EC) (Report of symptoms to PCP, recommendations to initiate preventive medications and make a specialist referral). (Subset of 12-16 year olds will all receive specialist care through telemedicine.)
4. To follow subjects prospectively throughout one year for endpoints defined by clinical outcomes (symptom severity, asthma control, and health care use), functional outcomes (absenteeism, quality of life), airway inflammation (FeNO), FEV1, and healthcare utilization. (Subset of 12-16 year olds will be followed for approximately 3 months.)

5. To assess the effectiveness of the TEAM-UP intervention in reducing asthma morbidity (including symptom-free days post-intervention as the primary outcome) compared to an enhanced care (EC) comparison group in school age children with moderate-severe asthma.
6. To assess the effectiveness of TEAM-UP in improving guideline-based asthma care (corrective actions; step-wise medication adjustments, identification and treatment of allergies or other co-morbid conditions) vs. EC.
7. To establish the cost-effectiveness of the intervention with a specific focus on ultimate sustainability and dissemination.
8. To evaluate the process of program implementation (i.e., convenience, scheduling, satisfaction, etc.)

Study Overview:

The overall goal of this project is to test a novel school-based program that links our effective school-based, primary care directed asthma management program with specialist-supported care for children requiring Step 3 or higher care. In partnership with caregivers and PCPs, specialist care will be facilitated via telemedicine, with management based on a tiered guideline-based stepwise approach. We will link children to existing community resources and will use school-based and/or video supported DOT to ensure adherence to therapies. This study includes a 2-group randomized trial to test TEAM-UP (***Telemedicine Enhanced Asthma Management - Uniting Providers***). All enrolled children (ages 4-12 yrs.) will be referred to their PCP for initiation of preventive asthma medication. Children randomly assigned to TEAM-UP will also have a telemedicine visit with a specialist provider after 4 weeks of initiating DOT as well as 2 follow-up visits to ensure optimal response to treatment. Collaboration with the PCP and the child's medical home will occur throughout the study period. We will enroll 360 children over four years from schools and primary care offices. We will assess the effectiveness of the program in reducing morbidity and improving guideline-based asthma care (primary outcome: symptom-free days at 3, 5, 7, and 12 months). At the study's completion, the effectiveness of this novel system of care will be better defined as a sustainable means to improve care and reduce morbidity for the highest risk children with difficult to control asthma. A subset of children (approximately 10-30 teens) ages 12-16 years will be enrolled to test the feasibility of TEAM-UP in older children.

Study Design:

This study includes a two-group randomized trial. Children referred to the study (through school medical alert forms and healthcare provider referrals) will be systematically screened for asthma severity or control, and 360 eligible children will be assigned randomly to either the TEAM-UP intervention (directly observed administration of preventive asthma medications and ongoing monitoring and tailoring of the care regimen using asthma specialist-directed telemedicine visits) or the EC comparison condition (asthma screening with symptom reports and guideline-based recommendations for preventive medications, as well as systematic feedback to the PCP and caregiver to promote appropriate follow-up care). Randomization will be stratified by 1) ever seeing an asthma specialist and 2) use of a preventive asthma medication at baseline. A permutated block design will be used to assure an equal balance of children in each group over time. Following randomization, children will be followed prospectively and systematically for one year.

Subjects and Setting:

Children 4-12 years of age living in the City of Rochester and surrounding suburbs will be screened for eligibility. A total of 360 children will be recruited into the study at the beginning of each school year over 4 years. Children from approximately 50 or more schools will participate and each child will participate over 1 year.

In addition to the 360 children that will be recruited into the study, we will also include 360 primary caregivers, as well as approximately 50 school nurses, school administrators, primary care providers, and specialist providers, for a total of approximately 770 subjects. For the subset of teen children, we will also enroll 10-30 teens (12-16 years) and their caregivers. The updated total will be approximately 830 subjects.

Inclusion Criteria [1 AND 2 AND 3 AND (4 OR 5) must be met]:

1. Physician-diagnosed asthma (based on parent report with validation from the child's physician).
2. Age ≥4 and ≤12 years. (Subset of 12-16 year olds)
3. Residence in the City of Rochester and surrounding suburbs, with a primary residence within the following zip codes: 14445, 14604, 14605, 14606, 14607, 14608, 14609, 14610, 14611, 14612, 14613, 14614, 14615, 14616, 14617, 14618, 14619, 14620, 14621, 14622, 14623, 14624, 14625, 14626.
4. For referrals from medical practices, if any of the 3 criteria below are met based on data obtained from a referral, then the child will be considered eligible due to their history of significant asthma and risk for future acuity, regardless of whether the caregiver-reported NHLBI symptom criteria (listed in #5 below) are met.
    i. ≥2 asthma exacerbations (resulting in ED, urgent Care, or acute clinic visits) in the prior year
    ii. ≥2 oral prednisone (systemic steroid) episodes in the prior year
    iii. ≥1 hospitalizations for asthma in the prior year
5. Moderate-severe persistent severity (requiring Step 3 or higher care) or difficult to control asthma despite therapy (based on age-specific NHLBI guidelines[10]).

    Moderate-Severe Persistent Severity (for children not taking a preventive medication)

    a. Age 4: Any 1 of the following:
        i. Daily asthma symptoms (in prior 4 weeks)
        ii. >2 days per month with nighttime awakenings
        iii. Daily use of rescue medications for symptom control (in prior 4 weeks)
        iv. >2 asthma episodes during the past 6 months that required systemic corticosteroids*
    b. Age 5-11: Any 1 of the following:
        i. Daily asthma symptoms (in prior 4 weeks)
        ii. >1 day per week with nighttime awakenings
        iii. Daily use of rescue medications for symptom control (in prior 4 weeks)
        iv. >2 asthma episodes during the past 6 months that required systemic corticosteroids*
    c. Age 12: Any 1 of the following:
        i. Daily asthma symptoms (in prior 4 weeks)

ii. >1 day per week with nighttime awakenings

iii. Daily use of rescue medications for symptom control (in prior 4 weeks)

iv. >2 asthma episodes during the past 6 months that required systemic corticosteroids*

*adapted from NHLBI guidelines and based on specialist recommendations

<u>Not Well Controlled</u> (for children taking a preventive medication)

a. Age 4: Any 1 of the following:

i. >2 Days/week with asthma symptoms (in prior 4 weeks)

ii. >1 day per month with nighttime awakenings

iii. >2 Days/week use of rescue medications for symptom control (in prior 4 weeks)

iv. ≥2 asthma episodes during the past year that required systemic corticosteroids

b. Age 5-11: Any 1 of the following:

i. >2 Days/week with asthma symptoms or multiple times a day on ≤2 days/week (in prior 4 weeks)

ii. ≥2 days per month with nighttime awakenings

iii. >2 Days/week use of rescue medications for symptom control (in prior 4 weeks)

iv. ≥2 asthma episodes during the past year that required systemic corticosteroids

c. Age 12: Any 1 of the following:

i. >2 Days/week with asthma symptoms (in prior 4 weeks)

ii. ≥1 day per week with nighttime awakenings

iii. >2 days/week use of rescue medications for symptom control (in prior 4 weeks)

iv. ≥2 asthma episodes during the past year that required systemic corticosteroids

Exclusion Criteria:

1. Inability to speak and understand English. (*Parents unable to read will be eligible, and all instruments will be given verbally.)
2. Current participation in an asthma study.
3. Planning to leave the Rochester area in fewer than 6 months.
4. If they have received asthma specialist care in the prior 3 months, they will be asked if they would be comfortable seeing an additional asthma specialist for our study if their current specialist is unable to participate in the study. If the family is not comfortable with seeing an additional asthma specialist for the study, they will be excluded. (For the subset of teens, this will not be an exclusion factor.

5. Having other significant medical conditions, including congenital heart disease, cystic fibrosis, or other chronic lung disease, that could interfere with the assessment of asthma-related measures.
6. In foster care or other situations in which consent cannot be obtained from a guardian.

Based on our prior studies, we anticipate <10% of subjects to be excluded based on these criteria.

Study Procedures:

Flagging and Screening Procedures:
Potentially eligible children will be identified through a variety of sources, including school asthma alert lists, school nurse referrals, and medical practices. We have used each method of recruitment successfully, with consistently high participation rates (>75%). The city school district routinely compiles "medical-alert" forms at the start of the school year, which include listings of children with asthma. School nurses or health aides will make referrals based on these lists or on frequency of visits to the nurse's office for rescue medication. In compliance with the Family Education Rights and Privacy Act, we have a Non-Disclosure Agreement with the school district that allows our study team to actively participate in this screening process.

Children also will be referred by their primary care or specialty practice based on electronic medical record or claims data, or by care coordinators in the practices. Referral forms will be available to each of the major practices in the city, and will be solicited monthly starting in the mid-summer. Once identified, someone from the practice (e.g., nurse, care coordinator, etc.) will introduce the study team to the family. For children in the study investigators' medical practices, TEAM-UP staff will contact caregivers by telephone on behalf of the investigators to explain the program and determine eligibility. We will also request a HIPAA waiver, allowing research staff access to medical records to review children's records and provider schedules to identify potentially eligible children. We have previously recruited from all of these practices.

Lastly, the study team may call families that have agreed to be contacted for future studies (RSRB#31010) to assess eligibility for the current study. This system of recruitment has been successful in our prior work and has allowed us to reach traditionally underserved children throughout the community. Enrollment will occur from mid-summer through January.

Baseline Assessment:
Following screening we will schedule a home visit to obtain informed consent from the caregiver and assent from children $\geq$8 years old. The baseline evaluation will include an assessment of asthma symptoms, standard family and health history variables and a home environmental assessment. The interview survey includes questions adapted from several validated scales (see below). An asthma symptom diary, developed using the school calendar, will be given to the family for tracking of symptoms throughout the school year. We will obtain height and weight measurements, as well as, saliva samples to measure smoke exposure through the biomarker cotinine. Lastly, we will obtain exhaled nitric oxide measurements using a portable NIOX VERO machine, to objectively measure airway inflammation, and will measure FEV1 using a portable spirometer. All surveys and questions will be read aloud.

For home interviews in which the child is not present, we will obtain the parent's permission to meet with the child at the school nurse's office to obtain assent (if necessary) and collect cotinine, spirometry,

and exhaled nitric oxide measures. The baseline assessment will include a detailed asthma medication reconciliation and verification of the child's insurance information.

In instances where a caregiver states that their child (age ≥8 years) is unable to provide assent to the study (e.g., a child with autism), the assent form will be waived and the research assistant will document the reason for the assent waiver in the subject's study chart.

If we are unable to conduct a home visit (e.g., concerns for COVID-19, safety, scheduling) to obtain consent, we will obtain the informed consent using electronic consent (eConsent) through REDCap. If eConsent is utilized, we will email or mail the consent, assent, and other forms to the family ahead of the baseline for their review. A study team member will use Zoom to meet with caregivers and children (with the option of telephone for caregivers of children younger than 8 years) to describe the study in detail, answer questions, and walk the family through the eConsent on REDCap (link sent via email or text messaging per family preference). If a family cannot access REDCap or Zoom, we will conduct a brief in-person visit either at the home or mutually agreed upon location, maintaining social distancing and using PPE for the family and the study staff (as outlined in the UR's Research Guidelines). For eConsent, we will collect child and caregiver names, dates of birth, and will establish a 4-digit pin with the family to confirm their identity on REDCap. We will email or mail (per family preference) the PDFs of the signed Caregiver Permission Consent Form, Verbal Assent Script, and other documents needed for the study (SH419TELE MR Telehealth Consent Form, Golisano Pediatric Telemedicine Consent Form, SH 48 GPED MR ARMI for Telemedicine, BOCES RCSD Permission to Administer Medication Form, and optional SH48GP Photo Image Release Form.)

In instances when the caregiver who provided consent is unavailable for follow-up and a different caregiver would prefer to respond to the follow-up assessments, the study will be described in detail and verbal consent will be obtained over the telephone from the new caregiver for completion of the follow-up survey. In rare instances where the child's primary caregiver changes, written consent will be obtained from the new caregiver.

Participants will be given the option to allow future contact for other research studies at the time of consent. All participants who provided permission will be added to a future contact database dedicated to childhood asthma research (RSRB #31010).

For the teen subgroup, we have requested a waiver of documented consent, as the data collection will be minimal, the intervention is to implement guideline-based care with specialists via telemedicine, and we will not be implementing directly observed therapy (DOT) in school, as we do for the younger children. We will obtain verbal approval from both the caregiver (screening script) and teen (assent script) for this subgroup.

Randomization:

After the baseline assessment, each child will be randomly assigned to either the TEAM-UP or EC group. Randomization will be stratified by 1) ever seeing an asthma specialist and 2) use of a preventive asthma medication at baseline. Due to the seasonality of asthma, we will use a permutated block design to assure an equal balance of children in each group over time. The randomization scheme will be independently developed by the Biostatistics Center, and will be implemented via REDCap™. All families will receive an educational packet including asthma information, smoking cessation resources, and information about local asthma and community resources. Once randomized, the research team will send a symptom report and notification of enrollment to each child's PCP (see below)

<u>All Study Children</u>:

For all enrolled children, we will contact the PCP by facsimile or email and will recommend preventive asthma medication as well as a referral to an asthma specialist. We will encourage the use of pharmacies with delivery (several local pharmacies routinely provide delivery services) with instructions indicating one canister of preventive medication, with a spacer and mask as appropriate, to be dispensed for home doses on weekends and days the child does not attend school, and a second canister for supervised medication administration at school on school days if needed. This system has been successful >95% of the time in our prior studies. We include the recommendation for daily preventive medication for all children, including those in the EC group, because we have established the effectiveness of consistent preventive medication use in our prior studies and it is well accepted as a care measure nationally. The specialist referral is consistent with guideline recommendations for children with this level of severity.

TEAM-UP Intervention:

Children randomly assigned to TEAM-UP will have a telemedicine assisted specialist visit scheduled after 4 weeks of initiating school-based and/or video supported DOT, as well as 2 subsequent follow-up visits. The visits will be performed by a specialist in pediatric asthma. Appointments will be scheduled in conjunction with the child's caregiver. If the visit is able to be prepared at school, health data will be collected by clinical telemedicine assistants (CTAs) who already work in the district. In these instances the CTA will bring the mobile telemedicine unit and meet with the child at school. If conditions allow, the CTA will obtain spirometry and FeNO readings, and then enter information regarding symptoms and triggers (collected at screening) into the system. Physical examination data will be uploaded (medical images, height/weight, breath sounds). Visits will either be conducted in real time using videoconferencing or information will be securely stored in the telemedicine system's "virtual waiting room" until a provider is ready to complete the visit.

Initial Telemedicine Asthma Control Assessment - The first telemedicine specialist visit will occur after 4 weeks of initiating school-based and/or video supported DOT to parallel routine scheduling processes (approx. 4 week wait time for specialist visits) and to allow for an accurate assessment of medication and care needs once adherence with a daily controller medication has been established. The specialist provider will log on to the telemedicine system from their office and perform the visit by reviewing the information collected, viewing images, and listening to breath sounds. The provider will communicate with the caregiver by videoconference or telephone to discuss the child's asthma and conduct a needs assessment. The primary goal of the ***initial visit*** will be to optimize the medication regimen based on guideline-recommended stepwise care. These children will already be receiving some form of DOT of a preventive asthma medication (most commonly an inhaled corticosteroid), however as per NHLBI guidelines for Step 3 or higher care, many will require a 'step-up' to a combined anti-inflammatory medication with a LABA (i.e.; Advair®), or addition of a LTRA[15-17] The specialist provider will also deliver asthma education (trigger avoidance, symptom monitoring, adherence promotion, proper medication administration technique) and an asthma action plan (AAP), and provide targeted referrals to community resources.

If the specialist has difficulty contacting the caregiver to complete the assessment and review the plan, they can request that the CTA or the primary care practice's care coordinators assist with communications. If the child is not attending school when a telemedicine visit is due, the visit may be prepared at the child's home, another childcare setting, or entirely remotely. This is consistent with the current telemedicine program's clinical protocol. The telemedicine assessments approximate care at an outpatient specialist visit; visits take approximately 30 mins.

Any new medications that are prescribed will be sent to pharmacies that routinely provide delivery services. Children will receive one medication dose daily through school if this is possible;[59] additional needed doses will be given at home by caregivers and adherence will be video supported. While many schools do not have a full time nurse, schools are prepared for daily medication administration when in session for in-person learning. In our prior study, medications were administered >95% of the time children were in school. All children will be instructed to rinse their mouth with water after each medication dose. Medication administration logs (school-based and/or video supported DOT) will be used for tracking.

A telemedicine visit summary will be sent to the PCP, with requests for feedback and input, and the PCP will continue to coordinate the care. The 3 major practices serving urban children in Rochester are certified as Patient Centered Medical Homes, and include care coordinators to assess barriers and facilitate access to services. Maintaining care through this system is critical to ensure continuity and unification of services. A visit summary and AAP will also be sent to the caregiver.

Follow-Up Telemedicine Asthma Control Assessments – Follow-up specialist-directed telemedicine assessments will occur twice during the study period; 4-6 weeks after the initial telemedicine visit, and again 4-6 weeks later. These visits will focus on further evaluation of symptoms to ensure the goals of therapy are being met, assessment of triggers or co-morbid conditions that might interfere with an optimal response to treatment, and continued asthma education. Medication optimization will again be considered as needed. The specialist will also assess for medication-related side effects (oral thrush, growth monitoring). Further, many of these children will have allergic asthma and may benefit from initiation of antihistamine medications, specific allergy testing, and possibly the use of a biologic medication (Omalizumab or Meplizumab). If allergy testing or a biologic medication are needed, an in-person visit will be recommended (allergy/laboratory testing cannot be feasibly conducted in schools). If a possible co-morbid condition is identified, visits for additional evaluation (i.e.; sleep studies, upper GI evaluation, etc.) will be scheduled. The specialist may also refer to community resources as needed (i.e.; Healthy Home Partnership for trigger assessment, New York State quit line for smoking cessation support, care coordination from the medical home for transportation assistance). Information regarding any changes in the regimen will be sent to the PCP through the telemedicine system.

Children who continue to have poor control at the final telemedicine visit will be referred for an in-person specialist visit for further evaluation and management. These visits will be facilitated as needed with the support of the child's PCP and medical home. We do not anticipate the opportunity to step-down therapy, since all children will have moderate to severe persistent symptoms at the start of the trial and guidelines recommend several months of optimal anti-inflammatory therapy. A natural time for discontinuing or stepping-down therapy occurs at the end of the school year when the children will no longer be receiving medications through school and/or video supported DOT. Approximately, two weeks prior to the close of the school year, we will notify specialist providers, PCPs and families that children receiving preventive medications at school no longer will receive medications through the study.

Monitoring for Treatment Fidelity*:*
The study team nurse will review telemedicine visit records after each visit to ensure completion by the specialist provider within 3 days, and to assess delivery of guideline-based care. Any concerns will be relayed back to the specialist provider. We will track delivery of medications, DOT, and show rates at needed in-person visits. We will also ensure ongoing communication with the PCP.

Subgroup of Teens

For a small subgroup (approximately 10-30 teens), we will test the feasibility of conducting the TEAM-UP intervention with teens. This subgroup will not be randomized. For all teens, we will initiate a telemedicine visit conducted within the school (or home) with an asthma specialist. Two follow-up visits will occur either with an asthma specialist or with an asthma nurse educator, to re-assess symptoms and ensure guideline-based care is implemented appropriately. As routine within the Telemedicine Program, the teen's PCP will be notified of all visits, severity of child as documented within the telemedicine visits, and any changes in care that are recommended through this program. Unlike the study for younger children, we will not implement DOT of medications as part of the program for teens, although the telemedicine provider may suggest DOT in their asthma care recommendations.

Enhanced Care (EC) Comparison Condition:

Similar to the TEAM-UP group, children in the EC group will receive a symptom assessment and asthma education materials at baseline, and we will contact the PCP by facsimile or email and will recommend daily preventive asthma medication as well as a referral to specialist. However specialist visits will not be facilitated through the study. We will also give providers a summary of the national asthma guidelines and a list of community resources including the Healthy Homes Partnership and the New York State quitline. We will provide systematic reminders to the family and PCPs to schedule recommended healthcare visits at the same intervals as the TEAM-UP group's telemedicine visits. Participants will not be blinded to group allocation; they will be told that they are randomly assigned to 2 different ways of approaching asthma management. In all of our prior studies, the EC group improved over time, creating a conservative bias.

Follow-Up Assessments:

The intervention will continue for 12 months. The effectiveness of the study will be assessed by interviews (telephone and in-person) with caregivers, objective measures, school data (absenteeism, medication administration, nurse visits, academic performance), and medical record review. Research assistants who are blinded to the subject's group allocation will conduct telephone calls with caregivers at 3, 5, and 12 months following the initial baseline to collect the follow-up data. At approximately 7 months, a home visit may be conducted. While the intervention will only last 12 months, we may follow subjects for up to 5 years post their enrollment into the study to collect additional outcome measures. These measures may include medical chart review or additional survey assessments with the primary caregiver. If additional surveys are conducted with the caregiver, we will request verbal permission from the caregiver prior to collecting survey data. We may also send reminders and schedule appointments through text messages and emails. Text messages will be formatted in a manner that provides research relevance in the absence of personal health information (PHI). We may use a limited data set when sending text messages that can include dates and times for visits or telephone call reminders.

Evaluations may be conducted with school health staff members who administered directly observed therapy to children enrolled in the program. Surveys will be distributed prior to the end of the study. Respondents will be asked to complete the survey within a 2 week window and return via fax, email or web-based survey with email invitation.

Healthcare providers whose patient(s) were enrolled in the program will also be asked to complete a short evaluation asking for feedback on the process. These surveys will be administered on paper and returned via fax and as a web-based survey with an email invitation. We will also conduct semi-

structured interviews with participating school health staff and healthcare providers to gather additional information on program acceptability.

At the conclusion of the study, we will ask school nurses, health aides, administrators, staff, primary care providers, and specialist providers to complete a brief survey and semi-structured interview regarding their views of pediatric asthma, child health, and study processes. We will request a waiver of documentation of consent for these participants. Approximately 50 school nurses, school administrators, primary care providers, and specialist providers will be asked to participate.

For the subgroup of teens, we will follow the families for approximately 3 months. We will assess for symptoms and healthcare utilization, as well as feasibility, acceptability and satisfaction with the program.

Qualitative Assessment:

After completion of their final primary study follow-up at 12 months, we will contact a subset of children and caregivers (approximately 30 child-caregiver dyads), to conduct semi-structured interviews via telephone, Zoom or in-person. Caregivers and children ≥10 at the time of the interview will complete a verbal consent prior to the in-depth interview. The 30-60 minute interviews will be audio recorded and participants will be paid $50 in the form of reloadable VISA gift card through the Advarra Payment System. The in-depth interviews are aimed to better understand the barriers and facilitators to guideline-based recognition, treatment and management of allergic rhinitis in children with asthma. In addition, the in-depth interviews will also explore health literacy experiences and a needs-assessment for asthma-related health information.

We will conduct a similar semi-structured interview with approximately 20-30 health care providers of child participants from the primary study. The healthcare providers will receive an email introduction and/or phone call introducing the study. A verbal consent will be read to the providers prior to the interview, and the providers will be given a $5 gift card (e.g., Starbucks, Amazon, etc.) for their participation.

Measures:

The table below summarizes the outcome measures and covariates that will be collected for this study. It includes how the data will be collected, validated scales/instruments used, and times of administration.

Clinical Outcomes	**Measurement Strategy**	**Time of Administration**
Symptom Severity	Caregiver interview, NHLBI guideline-based items Asthma Control Test (ACT)	Baseline, each follow-up Baseline, 7 month follow-up
Health Care Utilization	Caregiver interview – health care utilization survey Review of medical chart and pharmacy records	Baseline, each follow-up Conclusion of Study
Airway Inflammation	Objective measurement: FeNO	Baseline, 7 month follow-up
Pulmonary Function	Spirometry	Baseline, 7 month follow-up
Functional Outcomes		

School Absenteeism	Caregiver interview School record review	Baseline, each follow-up Conclusion of study
Quality of Life	Caregiver interview-*PACQLQ*	Baseline, each follow-up
Potential Mediators		
Adherence	Caregiver interview-*Horne Adherence Scale*	Baseline, each follow-up
Communication with Providers	Caregiver interview-PEPPI	Baseline, 7 month follow-up
Satisfaction with Medical Care	Caregiver interview-PSQ-18	Baseline, 7 month follow-up
Independent Variables		
Demographic, Medical Variables	Caregiver interview	Baseline
Caregiver Depression*	Caregiver interview-*CES-D*	Baseline, 7 month follow-up
Environmental Allergens	Environmental survey	Baseline
Secondhand Smoke	Caregiver interview Salivary Cotinine measurement	Baseline, each follow-up Baseline, 7 month follow-up
Process Evaluation		
Training of School Nurses, CTAs, and Providers	Time to train nurses to deliver DOT with proper inhaler technique, train CTAs for asthma assessments, and providers for reinforcement of guideline based asthma care	Ongoing tracking log
Medication Delivery to School	Tracking log of days required to deliver medications to school and home and initiate DOT; both at beginning of the study and for follow-up adjustments	Ongoing tracking log
Percent of Days Children Receive Medications via DOT	Nurse medication administration and video supported DOT records	Collected at the end of the school year
<u>RE-AIM Metrics</u> *Reach,* *Effectiveness,* *Adoption, Implementation, Maintenance*	 Response rate, participant characteristics Primary analysis (symptoms, absenteeism, quality of life) Semi-structured interviews: parents, nurses, administrators, PCPs, specialists Perceived Attributes scale (for school nurses, health aides, and administrators)	 Ongoing tracking log, screening/baseline Conclusion of study Conclusion of study Conclusion of study

	Medical record review Response rate and attrition tracking	Tracking log

**All Families will be provided a list of local mental health resources at the beginning of this study.*

Fraction of Exhaled Nitric Oxide (FeNO):

Fraction of Exhaled Nitric Oxide (FeNO) measurement is a non-invasive measure of lung inflammation. This inflammation could be caused by many factors including colds, pollutant exposures, and asthma. FeNO will be measured using the NIOX VERO® Airway Inflammation Monitor, an electrochemical hand-held device that instantly analyzes exhaled air for NO concentration. Children will be asked to first fully exhale and then to take a fast and deep inhalation through a disposable mouthpiece attached to the device. Then, we will ask children to exhale slowly and steadily through the mouthpiece. If done correctly, a reading will appear on the screen which will be recorded manually. FeNO will be measured at the baseline visit and then again at the 7 month follow-up. Some children may have difficulty with this procedure; we will only include data for children who are able to perform the procedure accurately.

Pulmonary Function:

To assess pulmonary function, we will use the EasyOne® Air portable spirometer, which meets American Thoracic Society standards for FEV_1, FEV_1 % predicted, PEF, and FVC at baseline and 7 month assessment. Some young children may have difficulty performing spirometry adequately; we will only include data that meet standard quality criteria.

Secondary Smoke Exposure: Saliva Sample Collection for Measurement of Cotinine:

Exposure to secondhand smoke will be assessed by both interview survey and cotinine measurements. At the beginning and at the 7 month follow-up, a member of the research team will collect salivary fluid samples from each child using the Sorbette fluid specimen collection device, which consists of a small sterile swab mounted on the end of a 5.5 cm plastic handle. Collection will be made according to a standard protocol developed for use with children. Salivary samples will be stored frozen and shipped via courier to Salimetrics, LLC in State College, PA for analysis. The cotinine results will be recorded as an outcome measure and will be available to families by request. All families will receive resources on how to stop smoking and prevent smoke exposure. We will not collect cotinine samples for the teen subgroup.

Compensation:

Each participating parent will be paid $50 after completion of the baseline assessment through Advarra Participant Payments. This payment system lets the participant choose from a reloadable debit card; direct deposit; or mailed paper checks. Subjects will also receive $20 reloaded onto their gift card after each of the telephone follow-up surveys and $50 reloaded onto their gift card after the 7-month follow-up assessment. Total payment will be no more than $160. Payment to participants will be in the form of a reloadable VISA gift card through Advarra Participant Payments. Healthcare providers who complete an evaluation at the end of the program will be mailed a $5 Starbucks gift card to thank them for their time. The subgroup of teens and caregivers will receive $25 after their baseline surveys and final surveys (up to $50 each). For a subgroup of children and caregivers, they will be paid $50 for their participation in the qualitative in-depth interviews. If participants have difficulty using the Advarra Participant Payment system, they will receive a different type of gift card of the same amount (e.g., Walmart).

There may be some cost to participate in this study. Participants will be responsible to purchase medications and spacers during the study, including those used for DOT of asthma therapy. Participants may be charged for using data on their smartphone in accordance with their personal phone data plan and rates. Participants randomized to the TEAM-UP group will also be responsible for any fees associated with telemedicine visits (e.g., co-pays etc.) completed through the study (these are medical processes that should occur according to the national guidelines regardless of the child's participation in the study). Based on our prior work with this population, we anticipate that most of the children will have some form of health insurance to cover the costs of visits and medications with minimal or no co-pay fee. In our prior studies we found that approximately 70% of families in the RCSD were insured with Medicaid which often eliminates co-pay fees for medications and care. If a child (in either group) does not have insurance, the study team will help the family secure health insurance. If a child in either group is unable to obtain health insurance and reports difficulty with associated medication costs, the study team will pay for the participant's medication and spacer for the program, as needed. If there is no insurance reimbursement for the telemedicine visit, subjects will not be asked to pay any additional costs. Participants and their insurance company will be responsible for the costs of all standard of care office visits and additional medications prescribed by their PCP.

Data Storage and Confidentiality:

To maintain the integrity, security, and confidentially of study data, the data will be maintained in a secure and encrypted web-based database and/or a password protected database on a secure university network drive. No subject data will be stored on the internal hard drives of any University of Rochester computers. After data validation and analysis, subject information will be de-identified. All consent forms, paper surveys and additional correspondence will be stored in a locked filing cabinet in a locked hallway or locked office, and will only be accessible by the study staff.

Baseline, follow-up, and chart review data will be entered into a password-protected Microsoft Access database. This database is stored on a secure university network drive that is only accessible by the research team whom must use their NetID and password to access the database. Data may also be collected using REDCap, which is a secure, password protected database (using University NetID's and passwords) hosted through the University of Rochester.

Portions of the assessments with caregivers, nurses, and healthcare providers may be tape recorded. These recordings will be saved on a University network drive that is only accessible by study personnel who must use their NetID and password to access these tape recordings. Once the recordings have been transcribed, they will be deleted from the network drive.

> The Rochester City School District has partnered with the University of Rochester study team for this study, and all of the procedures follow the school district's rules of privacy and confidentiality. As deputies of the school district, the study team is granted permission to review limited student information and contact families to inquire about their willingness to participate in the study.

Safety:

This intervention is designed to ensure guideline-based asthma care for children with uncontrolled asthma. This is ***not*** a drug investigational study since the effectiveness and safety of the recommendation medications are not being tested. The guideline-directed specialist visits and the preventive medications are recommended as the standard of care for children with the degree of symptom severity required for

enrollment into the program. The most common side effects of inhaled corticosteroids, including yeast infection of the mouth and facial rash, will be assessed during each follow-up interview. Any significant concerns will be relayed promptly to the study coordinator, the principal investigator, and the child's healthcare providers, the Institutional Review Board, the Data Safety Monitoring Board (DSMB, see below) and the NIH. There is a potential risk of adverse effects on linear growth from the use of inhaled steroids;[60] however, this risk is felt to be outweighed by the benefits for children with uncontrolled asthma including healthy lung growth/development and improved lung function. In general, these medications are well tolerated and safe.[61-63] Primary care providers and asthma specialist providers will prescribe all medications and must agree to follow the child for any potential side effects during the course of the study. In addition, the provider must agree to monitor the child's growth during the study period. Specialist providers may suggest additional testing and treatments for consideration. The specialist providers will review the risks and benefits of the any additional testing and treatments, and will ask for the caregiver's permission before initiating additional asthma treatments. Any child (in either group) experiencing an acute asthma exacerbation or experiencing worsening asthma symptoms at the time of a home visit or follow-up phone call will be referred immediately for medical care and will be referred to emergency services (e.g., 911) if symptoms are severe. As part of training, all research associates will be familiar with asthma medical alert symptoms. In either treatment arm, if the research associate observes acute asthma symptoms (consistent with yellow or red action zones on the Asthma Action Plan), the appropriate "action" (based on recommended asthma action plans) would be reviewed with the family and documented. In addition, school nurses are expected (per district school health services policies) to contact the parent of any child presenting to the nurse's office with acute symptoms and refer them promptly to their medical provider.

Further potential risks for families include breach of confidentiality as encountered with any study. We will take specific measures with data collection and storage to minimize any risks to the families. During visits and telephone surveys, research assistants will make efforts to protect subject privacy and confidentiality. The research assistants will ensure that the subject is comfortable answering questions and discussing the study prior to completion of consent/assent or any study measures. If it is suspected that someone in the home may cause serious harm to themselves or others, the study team will report these issues to the study coordinator and the principal investigator who may be mandated to report these concerns to appropriate authorities. There is also a risk that the study team may discover an unknown medical condition. If this is to occur, we will refer the family to their PCP or another appropriate health care professional for evaluation and treatment.

Patient privacy and the security of personal health information are important. Because the telemedicine application is browser-based, strong security has been implemented at both the originating (patient) sites and the provider sites. The telemedicine system utilizes the University of Rochester Medical Center's secure Electronic Medical Record (EPIC eRecord) and AMD Global Telemedicine's Telehealth Consult with AGNES Interactive software for media collection, transmission, and storage. Both the URMC's EMR and the AMD software meet or exceed security and confidentiality standards and are HIPAA compliant. The telemedicine software, data and server applications are encrypted, including file transfers, to protect the privacy of patients and ensure that application data are protected. The clinical telehealth assistants and providers are required to login to the mobile telemedicine unit, the EMR, and the AMD software using their own unique logins to maintain security and privacy of the data.

Video supported DOT will be accomplished through emocha® an established HIPAA compliant mobile app platform. This system uses virtual communication (e.g. asynchronous video technology and secure 2-way messaging) to support and encourage adherence through timely feedback and positive

reinforcement. The emocha® system allows for secure, temporary storage of encrypted videos on smartphones until a network connection is made to a secure server. Access to the emocha® app is protected by a secure password or PIN login and videos are not viewable in a phone's general media galleries. Only approved project staff from URMC and emocha® will have access to patient data. At the end of the study, the data will be stored with emocha® systems and the research team will be able to access data collected for up to 7 years for HIPAA compliance.

The study team will receive safety training yearly from key study personnel, and safety plans for home visits will be created (including traveling in pairs, safe words for emergency situations, and procedures for notifying and updating coordinators about whereabouts). These procedures are outlined in a team training manual given to all employees. The study team will also receive cultural awareness training from key study personnel prior to completing home visits.

We will protect the information provided by the teen subgroup as outlined above. Additionally, we will try our best to speak with the teen separate from caregiver (over the phone, or separate rooms), but this may not always be possible.

Data and Safety Monitoring:

Data Quality Monitoring

The research associates will be responsible for all data collected during the home assessments. They will receive training from key study personnel regarding asthma terminology, symptoms, and medication understanding. They also will be trained on the use of equipment for cotinine measurements, the EasyOne® Air spirometer, and the NIOX VERO® instrument for collection of exhaled nitric oxide. Baseline data forms will be completed electronically on laptop or tablet computers during the home visit. All data collected on laptops/tablets are entered using a secure and encrypted online database supported through the University of Rochester, and are only accessible to research staff using their University account login. For the safety of private subject information, no data will be stored on the laptops/tablets. For all of the follow-up interviews, data will also be collected using the same secure online database, and paper surveys will be used as back-up, if needed. Data forms will be returned with a cover sheet and other source documentation support materials (informed consent, contact information, etc.). Pre-intervention training of study staff will be conducted to increase knowledge about asthma, asthma medications, and other important information in order to reduce the number of "real-time" data collection errors. Through this training, staff will note any inconsistencies in parent reported data and will discuss them with the parent at the time of the interview.

A separate team of researchers will perform all follow-up interviews and follow-up data management. This group will work independently from the "enrollment team" and thus will be able to perform blinded assessments of outcomes. Our team, including the principal investigator, senior project coordinator, and recruitment and follow-up project coordinators, has an extensive record of high-quality data collection and management. We have tracked over 1,000 children in our prior randomized trials, and completed follow-ups with more than 90% of subjects. Randomization information will not be included with any follow-up materials in order to assure blinding of the outcome assessment.

Surveys will be reviewed by the coordinators, and any inconsistencies (misspellings, incorrect dates, etc.) will be corrected using telephone interviews with the parents. Simple range checks as well as cross-form validation checks will be performed to ensure the accuracy and completeness of the data. A list of all data checks performed will be maintained and any errors detected by this method will be noted on printed forms in red ink (initials and date of change). In addition, data forms, valid informed

consent documents for each enrolled patient, and supporting source documentation materials will be reviewed by the research analysts and coordinators for accuracy. Required regulatory documents (IRB approval, updates to the protocol, data monitoring documents) will be maintained by the senior coordinator. All events during the course of the trial including study enrollments, adverse events and study terminations will be reported to the senior coordinator.

Safety Monitoring Plan

Potential risks related to participation in this study are described in detail in the informed consent document. No investigational treatments or devices are used as part of this study. The risks of guideline recommended treatments include the risks of side effects with inhaled corticosteroids, as well as any treatments that will potentially be recommended by the specialist providers.

This intervention is designed to ensure guideline-based asthma care for children with uncontrolled asthma. This is ***not*** a drug investigational study since the effectiveness and safety of the recommendation medications are not being tested. The specialist visits and the preventive medications are recommended as the guideline-directed standard of care for children with the degree of symptom severity required for enrollment into the program. The most common side effects of inhaled corticosteroids, including yeast infection of the mouth and facial rash, will be assessed during each follow-up interview. There is a potential risk of adverse effects on linear growth from the use of inhaled steroids; however, this risk is felt to be outweighed by the benefits for children with uncontrolled asthma including healthy lung growth/development and improved lung function. In general, these medications are well tolerated and safe. Primary care providers and asthma specialist providers will prescribe all medications and must agree to follow the child for any potential side effects during the course of the study. Specialist providers may suggest additional testing and treatments for consideration. If allergy testing or immunotherapy is recommended, the specialist provider will review the risks and benefits of these procedures or treatments upfront. If a biologic therapy is recommended, the specialist providers will obtain written informed consent prior to any administration of these agents.

For all enrolled children, we will help families access medical care for the child's asthma if the family does not have a primary care provider. All study personnel who interact with families will explain their role (specifying that their role is not a substitute for medical care) at their initial meeting with the family and continue to encourage families to obtain care throughout the course of the intervention. We also will have a safety plan in place for any caregiver reporting that the child (in either group) has worsening asthma symptoms. These children will be referred immediately for medical care and will be referred to emergency services (e.g., 911) if symptoms are severe. As part of training, all research associates will be familiar with asthma medical alert symptoms. In either treatment arm, if the research associate observes acute asthma symptoms (consistent with yellow or red action zones on the Asthma Action Plan), the appropriate "action" (based on recommended asthma action plans) would be reviewed with the family and documented. In addition, school nurses are expected (per district school health services policies) to contact the parent of any child presenting to the nurse's office with acute symptoms and refer them promptly to their medical provider.

Any significant adverse events will be flagged by the follow-up team and relayed promptly to the study coordinator, the principal investigator, and the Institutional Review Board within 24 hours, and to the DSMB and NIH as per protocol. All study records will be kept strictly confidential as required by the policies and procedures of the University of Rochester where data are collected, processed, or reported. The family can discontinue their participation at any time during the study.

If a caregiver reports significant depressive symptoms or unusual circumstances (i.e., difficulty providing food or shelter for the family), we will offer the caregiver mental health or community resources and encourage the caregiver to contact their physician, a resource, or other trusted party. If at any time during the study a child or caregiver expresses active suicidal or homicidal ideation, this information will be promptly reported to the proper authorities, and mental health referrals will be given to the family as is appropriate.
All records will be kept strictly confidential as required by the policies and procedures of the University of Rochester where data are collected, processed, or reported.

A Data Safety Monitoring Board (DSMB) including a pulmonary specialist (Elizabeth Allen, MD; Division of Pulmonary Medicine, Nationwide Children's Hospital), a general pediatrician and health services researcher (Ian Paul, MD, MPH; Division of General Pediatrics, Penn State College of Medicine), and an epidemiologist (Susan Fisher, PhD; Temple University), has been assembled to provide ongoing oversight of the study. The DSMB will meet at least annually to review study procedures and data. The intervention will enhance access to care by enabling telemedicine specialist providers to implement guideline-based treatments for the children, and will only suggest daily medications that are routinely recommended by national guidelines for asthma care. The risks of any recommended treatments will be discussed in detail with the caregivers. In our previous school and office-based asthma programs, which included more than 1,000 children, there were no reports of significant adverse events related to the studies. The frequency and severity of all reported adverse events will be systematically recorded at each follow-up interview. Telephone interviewers will inquire about any adverse events, and specifically ask about any yeast infections of the mouth and facial rashes. We will also inquire about any worsening of asthma symptoms. We will hold weekly research review meetings with the study team to provide an additional layer of monitoring to ensure subject safety as well as treatment integrity. The board shall determine safe and effective trial conduct and recommend termination of the trial if significant risks develop or the trial is unlikely to be concluded successfully.

Potential Benefits:

Potential benefits of this intervention exist for both groups of children (TEAM-UP and EC). Children in the TEAM-UP group will be receiving an intervention to promote appropriate, step-wise, guideline-based care for their asthma. They may experience a reduction in respiratory morbidity due to guideline-based preventive actions (prescription of medications, counseling regarding triggers, treatment of comorbid conditions, etc.). Although families in the EC group will not receive telemedicine visits through the study, the families and primary care providers will receive reports about the child's severity and a recommendation for specialist care, and families will receive 3 reminders that their child should be seen for ongoing asthma care. Furthermore, children in both groups will be recommended to receive daily preventive asthma medications. At follow-up, any child with persistent symptoms or poor control will be referred back to their provider for ongoing care. It is possible that discussions with the study team may increase the parent's awareness of symptoms and actions may be taken resulting in reduced morbidity for these children.

Analysis:

Sample Size and Power Justification:
This study is designed to have adequate power to test the primary hypothesis that children in TEAM-UP will have more symptom-free days at 3, 5, 7, and 12-months compared to EC. Based on our prior data of patients with moderate to severe persistent symptoms, we estimate a pooled standard deviation (SD) of

SFD to be 3.6 and within-subject correlation (ICC) of 0.3. We calculated power for the intervention effect on SFD while justifying repeated assessments for outcomes. [64,65] A sample size of 150 subjects per group will obtain 90% power to detect a difference of 0.8 SFD, and 80% power to detect a difference of 0.7 SFD at a two-sided 5% significance level. This difference would be clinically meaningful and consistent with prior successful interventions. [7,66-68] We found that 194 of the children from our prior SB-TEAM study had moderate-severe persistent or difficult to control asthma at baseline, and would be eligible for TEAM-UP. In addition, in our prior office-based study we enrolled >400 children with moderate-severe asthma from the main primary care practices in urban Rochester over 4 years. Our prior studies enrolled >70% of eligible subjects. Thus, we can conservatively enroll 90 subjects/year, which is more than adequate for sample size requirements. We anticipate <15% attrition (attrition <5% in prior studies). We therefore expect complete data on at least 150 children per group.

Primary Analysis:

The primary analysis of this study aims to assess the effectiveness of the TEAM-UP intervention in reducing asthma morbidity (including symptom-free days post-intervention (follow-ups at 3 mo, 5 mo, 7 mo and 12 mo as the primary outcome) compared to an enhanced care comparison group in school age children with moderate-severe persistent asthma or uncontrolled asthma. We will use graphs and descriptive statistics to summarize the primary and secondary outcomes by intervention group at each assessment point (baseline, 3, 5, 7 and 12 mos). We will assess for differences between groups at baseline despite randomization in key characteristics (i.e.; age, race, ethnicity, insurance, caregiver education, smoke exposure.) These comparisons will enable the identification of covariates to be controlled when evaluating the treatment effect. If distributional assumptions associated with a particular statistical procedure are violated, appropriate transformations will be made or non-parametric alternatives used. In accordance with the intention-to-treat principle, [69] all randomized subjects will be analyzed within the group to which they were assigned. Minimal crossover is expected. Hypothesis-driven comparisons will be made to control the family-wise type I error rate at 0.05 (two-sided) for the primary hypothesis.

For the primary outcome analysis, the time-course of treatment effect on SFD during the follow-up period will be evaluated using a linear mixed model (LMM) accounting for repeated measures within each subject to test the intervention effect of TEAM-UP over time, with SFD as the dependent variable, and intervention group and group by time interaction as independent variables. [70] The treatment effect will be regarded as fixed and the subjects as the random effect, with appropriate variance covariance structure specified. Interaction effects between intervention and follow-up periods are included to catch possible differences in how SFD changes over time between intervention groups. Post treatment effects and maintenance gain from short to long term will be assessed by specifying appropriate linear contrasts. Baseline SFD and factors that differentiate between groups will be included as covariates. Model fitting statistics such as Information Criteria and difference in log likelihood will be used for model selection. Standard measures such as residual plots will check goodness-of-fit of the regression model assumptions and identify outliers. We will calculate intraclass coefficient (ICC) within providers (specialist and PCP); if autocorrelation is significant, provider will be included as another level of random effect in the mixed model to account for the nested data structure. If the outcome measure violates the normal assumption required by LMM, we will evaluate the intervention effect using Generalized Estimating Equations (GEE). [71] By specifying marginal mean effects of independent variables on the outcome variable, GEE offers consistent and robust estimates but does not require specification of a fully parametric distribution. Other continuous outcomes (days/nights with symptoms, quality of life, etc.) will be analyzed similarly. Discrete outcomes will be analyzed by fitting Generalized Estimating Equation model. Appropriate link functions and response probability distributions will be specified.

We will also consider whether certain process measures from our conceptual framework (guideline-based corrective actions, adherence, patient/provider communication, satisfaction with care) act as mediators in the relationship between the intervention and outcomes. [72] Thus we will estimate both the direct intervention effect on outcomes, as well as the indirect effect through mediators. For each purported mediator, we will use structural equation models (SEM)[73] to model its relationship to treatment and primary outcome. Maximum Likelihood (ML) will be used for estimation. Goodness-of-fit will be assessed in a two-level process. In the first level, the fit of the unrestricted model will be tested using standard diagnostic measures for linear regression. In level two, the appropriateness of assumption of the proposed structural equation model will be investigated by testing this model against the unrestricted model. The following indicators will be used:[74] (a) Comparative Fit Index (CFI), (b) Non-Normed Fit Index and (c) Root Mean Square Error of Approximation.[75]We will use chi-square statistics for the structural invariance tests to determine effect modifiers. These analyses will aid in our understanding of pathways by which TEAM-UP impacts outcomes.

The primary analyses will include all randomized subjects. Substantial attention will be invested in participant retention; reasons for any withdrawals that may occur will be documented. Missing data patterns will be examined by comparing subjects who discontinued with those who remained in the study. Inference based on the proposed methods GEE and/or LMM is valid provided that missing data follows the missing completely at random (MCAR) assumption. However, if the occurrence of missing data depends on the observed response but is independent of unobserved data (MAR), weight GEE (WGEE) will be used. Sensitivity analysis to the MAR assumption will also be carried out by modeling the between-group difference using WGEE.[76,77] Separate secondary per protocol analyses will be performed and interpreted with caution.

Cost Effectiveness Analysis:

We will consider the total cost of initiating and maintaining the program as well as the incremental cost-effectiveness ratio (ICER) of TEAM-UP versus EC. The ICER is the difference in cost between the 2 study groups relative to the difference in the number of SFDs gained between the 2 groups. The main outcome for the analysis from the societal perspective will be the ICER, defined as: *∆Medical+∆Productivity+$Program)/∆SFD*, where *∆=(TEAM-UP)-(EC)*. We will bootstrap[78] the ICER to estimate standard error and to evaluate uncertainty around the point estimate. We will compare the ICER to similar estimates from the literature. [79,80] We will plot an acceptability curve, linking various values of SFD to the probability of TEAM-UP being cost-effective. [81] The study from the Medicaid perspective will use the cost-benefit approach to economic evaluation. Benefits include the net difference in medical costs between children in TEAM-UP and EC and account for a potential reduction in unplanned visits as well as an increase in preventive visits. The cost is equivalent to the cost of the program (*Net Monetary Benefit=∆Medical-$Program)*.

Process Evaluation:

Descriptive statistics will be used for the process evaluation, looking in particular at the efficiency of the program implementation along with the responses from parents, PCPs, specialists, and school nurses and administrators about convenience, scheduling, satisfaction, and sustainability. [82,83] We will evaluate RE-AIM (*Reach, Effectiveness, Adoption, Implementation, Maintenance*) metrics to evaluate the program. To estimate *Reach* we will determine the proportion of eligible children with moderate-severe persistent asthma who participate, and will use data from screening forms to characterize those who do and do not participate. To estimate *Effectiveness*, we will conduct intent to treat analyses of the primary outcome (SFD), absenteeism, and quality of life. We will use school data as well as surveys from PCPs,

specialists, and school members to evaluate *Adoption*. We will conduct a survey of providers and school staff following the intervention to gauge their reaction to the intervention components and their willingness to support them in the future. To assess *Implementation* we will use check-lists, tracking logs, surveys and chart reviews to measure the extent to which participants partook in each program component (telemedicine visits, guideline-based adjustments, % medication doses delivered at school, and/or through video supported DOT). To assess *Maintenance* we will use surveys and open-ended questions to evaluate plans for continuation (or modification) of each intervention component post-study, and we will use 12-month follow-up data to analyze long-term effects on primary outcomes and QOL.

COVID-19

In response to the COVID-19 pandemic, we will follow the Human Subjects Research guidelines outlined by the University of Rochester to continue enrollment for this study. Please find the following link for these guidelines: https://www.urmc.rochester.edu/coronavirus/coronavirus-research/guidance-for-researchers/human-subjects-research.aspx. We will minimize in-person contacts to only those tasks necessary to conduct the research (e.g., obtaining consent, review medications and forms). We will ensure that team members are appropriately trained in safety measures, maintain social distancing when possible, use personal protective equipment for themselves and research subjects (and family members), and will ensure proper cleaning/sanitizing of hands, equipment and workstations. We will continue to monitor and follow the updated guidelines put forth by the UofR in the link above.

The intervention may look different during the COVID-19 pandemic. If schools are open, participants in the Intervention group may receive directly observed therapy (DOT) of their preventive asthma medication supervised by the school nurse or health aide. Additionally, they may receive telemedicine visits at school. However, if schools are not fully open or by family preference, we will support families with ongoing medication adherence, which will include school-based and/or video supported DOT. Additionally, providers may conduct telemedicine visits without the data obtained by clinical telehealth assistants onsite using Zoom or another HIPAA compliant method to remotely connect with families.

During the COVID-19 pandemic, the research team will not collect breathing measurements (spirometry and FeNO) as planned during the baseline or 7-month survey time point. When the pandemic has subsided, we will submit a protocol modification to re-start these collections.

We've included a brief, optional survey to assess how the COVID-19 pandemic is affecting children with asthma and their families. We will ask the caregivers if they would be willing to answer these questions at the end of follow-up surveys that we are already conducting.

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